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A convenient one-pot synthesis of Series of 1, 5-Benzodiazepine Derivatives under Solvent free Condition

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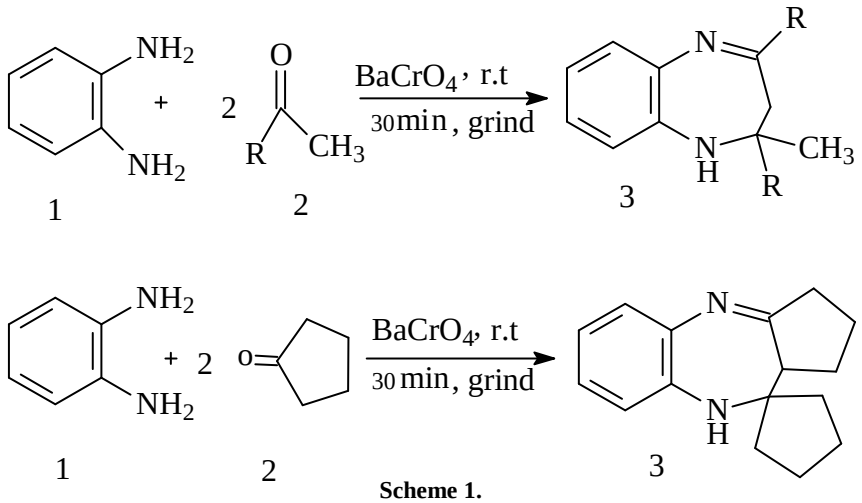
ABSTRACT

2, 3 Dihydro-1*H*-1, 5-benzodiazepines are synthesized by reaction of *o*-phenylenediamine with ketones under mild and solvent free conditions in the presence of catalytic amount of Barium chromate in short reaction time with excellent yield.

Keywords 1, 5-benzodiazepines, ketones, *o*-phenylenediamine, Barium chromate.

INTRODUCTION

Benzodiazepines and their derivatives are potentially important class of medicinally active compounds and have been widely used as anti-anxiety, tranq-uilizing, anti-inflammatory, anti-convulsant, anti-bacterial, analgesic, sedative, anti-depressive and hypnotic agents.[1,2] Benzodia-zepines are also used against viral disease, e.g. AIDS[3] and cardiovascular disorder,[4] Some benzodiazepine derivatives are used in fine chemical industries such as photographical dyes for acrylic fiber,[5] they are also utililized in the synthesis of fused ring benzodiazepines class of compounds like triazolo,oxadiazolo,oxazino and furano-benzodiazepines.[6] Because of their important therapeutic value they have diverted the attention of chemist worldwide. A survey of literature reveals that the several synthetic methodology have been introduced for their synthesis, these include condensation of *o*-Phenylenediamine with α-β unsaturated carbonyl compounds,[7] β haloketones,[8] or Ketones in the presence of BF_3OEt,[9] $NaBH_4$,[10] PPA- SiO_2,[11] MgO-$POCl_3$,[12] $Yb(OTf)_3$,[13] Amberlyst-15,[14] and $Ag_3PW_{12}O_{40}$,[15] solid super acid sulphated zirconia,[16] acetic acid – under MWI,[17] $AgNO_3$,[18] ionic liquid,[19, 20]and zinc montmorilonite as catalyst at r.t.[21] However few of these methodologies have several disadvantages such as harsh reaction condition, long reaction time, expensive reagents, low yield, tedious workup and formation of side products. Keeping in mind the above consideration we herein develop a one pot synthesis of 1, 5-benzodiazepines by condensation of *o*-Phenylenediamine with ketones under solvent free conditions catalyzed by barium chromate. (Scheme-1).



Scheme 1.

RESULTS AND DISCUSSION

Barium chromate is a cheap and readily available reagent it efficiently catalyze the condensation of ketones with *o*-phenylenediamine at room temperature, under solvent free conditions, in short reaction time (30 min) with excellent yield of the product. In the current strategy, *o*-phenylenediamine, cyclic /acyclic ketones and catalytic amount of barium chromate were ground well using mortar and pestle, diluted with ethyl acetate and then stir at room temperature, the series of corresponding1, 5 benzodiazepines and fused ring benzodiazepine derivatives were obtained in 80-88% yield. Completion of the reaction was monitored by TLC.The results are summarized in Table 1. The structures of the products were confirmed by their M.P, I.R, Mass and H^1NMR spectroscopy data and found to be in agreement with the values reported in the literatures.

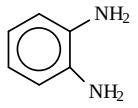
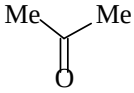
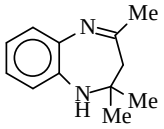
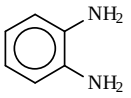
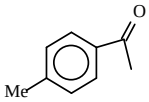
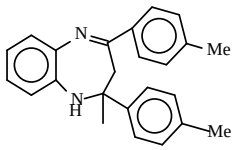
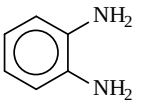
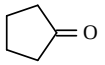
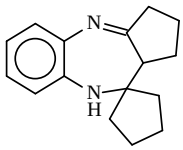
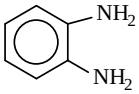
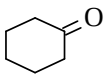
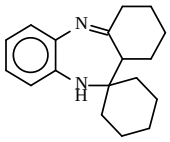
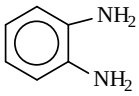
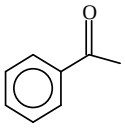
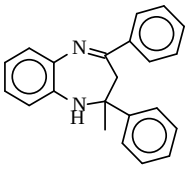
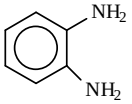
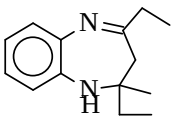
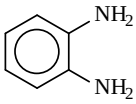
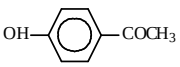
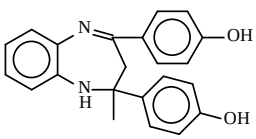
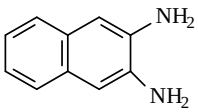
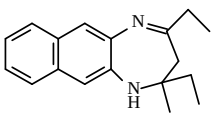
Typical Procedure for the synthesis of 2, 3 Dihydro-1*H*-1, 5-benzodiazepines

A mixture of *o*-phenylenediamine (10 mmole), ketones (20 mmole) and Barium chromate(catalytic amount) were ground well using mortar and pestle, the reaction mixture was then diluted with ethyl acetate and stir for 30min, after completion of the reaction {monitored on TLC, eluent: ethyl acetate: pet ether (3:7)}, the solvent was removed by distillation under reduce pressure. The crude product was purified by column chromatography, which was further purified by recrystallisation using ethyl alcohol. The reaction proceeds efficiently under ambient Conditions giving good to excellent yields of 1, 5-benzodiazepines.

EXPERIMENTAL

All H^1 NMR spectra were recorded in $CDCl_3$ on a Brucker AC 200 and Brucker MSL 300 spectrometers and chemical shift were reported in ppm downfield from tetra methyl silane. Infrared spectra were recorded on a PerkinElmer infra red spectrophotometer using KBr discs, TLC was performed on silica gel coated aluminum plates using ethyl acetate and pet ether (3:7 v/v) as eluent, melting points were determined on an electronic melting point apparatus and were uncorrected.

Table1: Barium chromate catalyzed synthesis of1, 5-Benzodiazepines under solvent free conditions. All the reactions were completed in $_{30}$min.

Entry	Substrate{$_1$}	Ketone{$_2$}	Products{$_3$}	Yield(%)	M.P(^{o}C)
1				80	138-139
2				85	150-152
3				85	136-138
4				85	138-140
5				85	150-151
6				80	144 -146
7				85	150-152
8				80	218-220

Spectral data of the selected products {entry 1, 2, 7}

1. IR (KBr): 3389 cm^{-1}, 2970 cm^{-1}, 1631cm^{-1},1591 cm^{-1},1470 cm^{-1},1100cm^{-1}, 744 cm^{-1};
   H^1 NMR ($CDCl_3$): δ 1.1 (s, 6H), 1.8 (s, 2H), 2.0 (s, 3H), 3.6 (brs, 1H), 5.9-7.0 (m, 4H); MS (m/z):188 (M^+)
2. IR (KBr): 2922 cm^{-1}, 1600 cm^{-1}, 1356cm^{-1},746 cm^{-1}
   H^1 NMR ($CDCl_3$): δ 2.13 (s, 6H), 1.24 (s, 3H), 2.4 (d, 1H, J=6.9 Hz), 2.5 (d, 1H J= 6.9 Hz), 3.67 (brs, 1H), 6.0-6.66 (m, 4H), 6.72-7.2 (m, 8H);
7. IR (KBr): 3377 cm^{-1}, 1631 cm^{-1},1440 cm^{-1};
   H^1 NMR ($CDCl_3$): δ 1.3 (s, 3H), 2.2 (d, 1H, J=6.9 Hz), 2.49 (d, 1H, J=6.9 Hz), 3.6 (br s, 1H), 8.4 (s, 1H), 8.87(s, 1H), 6.3-6.7 (m, 4H), 6.8-7.2 (m, 8H)

CONCLUSION

In conclusion, it can be summarized that we have develop a new, mild and efficient method for the synthesis of 1,5-benzodiazepines.The workout is easy, inexpensive catalyst, no solvent is required, reaction time is short, reaction conditions are mild and yield are excellent.

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